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Joana Filipa Lopes Figueiredo de Carvalho Paulo

Renal Sympathetic Ablation

New approach of hypertension therapy

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NOME

Joana Filipa Lopes Figueiredo de Carvalho Paulo

CARTÃO DE CIDADÃO	E-MAIL	TELEFONE OU TELEMÓVEL
13760799	joana_paulo_@hotmail.com	963216814 / 910820813

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Renal Sympathetic Ablation - New approach of hypertension therapy

ORIENTADOR

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Assinatura conforme cartão de identificação: Joana Filipa Lopes Figueiredo de Carvalho Paulo

Renal Sympathetic Ablation

New approach of hypertension therapy

Joana Paulo

Faculty of Medicine of the University of Porto (FMUP)

Al. Prof. Hernâni Monteiro 4200-319 Porto, Portugal

e-mail: mimed08097@med.up.pt /

joana_paulo_@hotmail.com

Telephone: 00351 963216814

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LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
CKD	Chronic kidney disease
DBP	Diastolic blood pressure
ESH/ESC	European Society of Hypertension/European Society of Cardiology
GFR	Glomerular filtration rate
HF	Heart failure
HT	Hypertension
HR	Heart rate
LV	Left ventricular
NA	Noradrenaline
RFA	Radiofrequency ablation
RH	Resistant hypertension
RSD	Renal sympathetic denervation
SBP	Systolic blood pressure
SNS	Sympathetic nervous system

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ABSTRACT

Hypertension is the most common attributable risk factor for stroke and myocardial infarction, leading to death when inappropriately treated. Despite the wide pharmacological available selection, blood pressure remains uncontrolled in a significant proportion of patients. Resistant hypertension is an increasingly common clinical condition, defined by blood pressure ≥140/90 mmHg (or ≥130/80 mmHg in diabetes or renal Insufficiency) regardless concurrent use of 3 or more antihypertensive drugs from different classes, including one diuretic, all at the optimal doses.

As patients with hypertension are at elevated risk for cardiovascular morbidity and mortality, this review summarizes the available data, based on bibliographic research using PubMed's data base, of new interventional approaches taking into account renal sympathetic activation's role in hypertension pathogenesis.

Renal Sympathetic Denervation is a novel catheter percutaneous procedure based on a therapeutic old concept which intends to ablate the nerves in order to interrupt the central nervous system and kidneys' bidirectional connection. So far, trials have demonstrated convincing and safe blood pressure-lowering effects in majority of treated patients. Moreover, potential additional benefits on hypertension's comorbidities, such as left ventricular hypertrophy and renal impairment, have been identified. Although this current evidence is mainly based on ablation through radiofrequency energy, several second-generation catheters have been developed aiming at safety and efficacy improvement.

Therefore, renal sympathetic denervation appears as a future potential hypertension treatment option, despite being already conducted, under severe controlled conditions, in some countries.

KEYWORDS

Blood pressure; Radiofrequency ablation; Resistant Hypertension; Renal Sympathetic Denervation; Sympathetic nervous system activity

RESUMO

A Hipertensão arterial é um dos principais fatores de risco para Acidente Vascular Cerebral e Enfarte do Miocárdio, resultando em morte quando não tratada. Apesar da vasta variabilidade farmacológica, a pressão arterial permanece incontrolada numa significativa percentagem de doentes. A Hipertensão resistente é uma situação clínica cada vez mais frequente, definida como pressão arterial ≥140/90 mmHg (ou ≥130/80 mmHg em caso de Diabetes ou Insuficiência Renal) apesar do uso concomitante de pelo menos 3 anti-hipertensivos de diferentes classes, incluindo um diurético, todos em doses adequadas.

Visto que os doentes hipertensos apresentam um risco elevado de morbilidade e mortalidade cardiovasculares, esta revisão reúne a informação disponível, com base em pesquisa bibliográfica através da PubMed, de novas intervenções baseadas na influência do sistema simpático renal na patogénese da Hipertensão.

A Desnervação Renal é um novo procedimento percutâneo fundamentado pelo antigo conceito terapêutico de ablação que interrompe a conexão bidirecional entre o sistema nervoso central e os rins. Até ao momento, os estudos têm demonstrado efeitos significativos e seguros na diminuição da pressão arterial na maioria dos indivíduos tratados. Para além disso, potenciais efeitos adicionais nas co-morbilidades da Hipertensão, como a Hipertrofia Ventricular Esquerda ou Disfunção Renal, têm sido detetados. Apesar da atual evidência ser baseada sobretudo na ablação por radiofrequência, vários cateteres têm sido desenvolvidos com o objetivo de melhorar a eficácia e segurança do procedimento.

Assim, a Desnervação Renal apresenta-se como uma potencial futura opção para o tratamento da Hipertensão, apesar de já ser utilizada em alguns países, em situações muito específicas.

PALAVRAS-CHAVE

Ablação por radiofrequência; Atividade do sistema nervoso simpático; Desnervação simpática; Hipertensão resistente; Pressão arterial

INTRODUCTION

Hypertension (HT) is a growing worldwide public health problem with an overall prevalence around 30-45% of the general population, with a steep increase with ageing attaining 65% in those over 60 years of age.[1] Since 2003 HT is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg.[2] It is recognized as the leading risk factor for cardiovascular and cerebrovascular disease, renal and visual impairment and death.[3] Cardiovascular risk is linearly related to blood pressure (BP) levels, doubling with every 20/10 mmHg increase in SBP/DBP, beginning at 115/75 mmHg. Thereby, it is considered to be responsible for more than 7.5 million deaths annually in the world.[4] A study conducted in 2003 showed that 42.1% of the Portuguese adult population aged 18-90 years had HT with a prevalence of approximately 79% in patients older than 64 years. Among hypertensive subjects only 11.2% achieved adequate BP control.[5]

HT can be primary (without apparent cause) or secondary to an identified etiology. The last, seldom diagnosed, is potentially curable or at least sensible to treatment with cardiovascular risk decrease.[1] The most common between these causes are obstructive sleep apnea, chronic renal disease (parenchymal and vascular) and primary hyperaldosteronism. Cushing's syndrome, pheochromocytoma, hyperparathyroidism and aortic coarctation are less frequent causes.[3] On the contrary, in most patients several factors contribute to disease's development.[6] Regardless the availability of several effective and safe antihypertensive treatment options, BP remains uncontrolled in a significant percentage of patients (approximately 50%).[3,7,8] Table 1 discloses some patient characteristics associated with resistance to HT treatment.

According to 2013 ESC/ESH recommendations and 2008 American Heart Association, resistant hypertension (RH) is defined as the inability to reach an effective BP control (<140/90 mmHg and <140/85 mmHg or <140mmHg in case of diabetes and renal insufficiency, respectively) despite the association of at least 3 antihypertensive agents with different action mechanisms, one of these

being a diuretic, at the maximum tolerated dosage.[1,3] Some authors also argue that patients whose BP is controlled with 4 or more medications are considered to have RH.[9]

Pseudoresistant HT apparently includes treatment-resistant cases (poorly controlled BP) which are, however, attributed to other factors.[10] Consequently, the RH concept rejects secondary forms, inefficient BP measurement technique, poor drug and lifestyle approach adherence and inadequate treatment strategy.[11] Moreover, this clinical condition should only be established when the uncontrolled BP is confirmed to be permanent through 24h-ambulatory BP monitoring (24h-ABPM) [12] with a mean threshold of SBP ≥130 and/or DBP ≥80 mmHg. This monitoring is essential to exclude pseudoresistance like white coat HT. RH has a multifactorial etiology and its exact prevalence remains unknown, varying from 5% to 30%.[1,11]

In the past decades the Sympathetic Nervous System (SNS) has been recognized as a central player in the cardiovascular homeostasis[13] and its enhanced activity has been established as a major contributor to chronic BP elevation.[6] It is also well known that kidneys' sympathetic innervation plays a major role in the pathogenesis of HT through modulation of renin's secretion, glomerular filtration rate (GFR) and renal absorption of sodium. Based on constantly higher heart rates and absence of response to intensive diuretic treatment among patients with RH, some authors suggested that treatment failure may be due to neurologic mechanisms like sympathetic overactivity. This differs from the traditional assumption that RH is mainly due to persistent hypervolemia.[10]

Therefore, considering the high prevalence of RH worldwide, the limited efficiency of pharmacological agents and the significant risk of accelerated cardiovascular mortality[11], new therapeutic procedures targeting the SNS have been developed in order to correct or at least slow down the pathological mechanism. One of these new and refreshing interventional approaches is the Renal Sympathetic Denervation (RSD). This review outlines the impact of renal sympathetic activity on BP regulation, the recent evolution of RSD therapy on RH treatment and its future potential applications.

METHODS

The present review was written based on bibliographic research using PubMed's data base. The search was conducted based on MeSH terms using the following combinations: hypertension, blood pressure, autonomic denervation, catheter ablation, sympathectomy, sympathetic nervous system.

HYPERTENSION TREATMENT

Nowadays, essential HT therapy is based on lifestyle modifications and pharmacological agents. The former is based on both dietary adjustments with salt restriction (5-6 g per day is recommended) associated with high consumption of vegetables and fruits and regular exercise practice (at least 30 minutes of moderate dynamic exercise on 5 to 7 days per week is recommended) leading to weight reduction (of BMI to 25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women is recommended, unless contraindicated). Moreover, smoking cessation and moderation of alcohol consumption (no more than 20-30 g and 10-20 g of ethanol per day in men and women, respectively) are essential for BP control.

According to 2013 ESH/ESC Guidelines the major advantage of pharmacological therapy is BP-lowering *per se* regardless the drug class of first line used, since all medications present similar effects and particular contraindications. Nevertheless, it must be taken into account both the adverse side effects and specific conditions in which some drugs have been proved to be more effective. The most used agents for the initiation and maintenance of therapy, contraindications and specific conditions to use each class are described on table 2. Combination therapy success has been attested not only in BP-lowering (possible synergism) but also in therapy compliance (single tablet) and side effects' avoidance. Therefore, it is recommended initiation with combined therapy in patients with high cardiovascular risk or considerably high baseline BP.[1]

The new algorithm purposed by the Eighth Joint National Committee[14] for the management of HT is exposed on figure 1. According to this Committee, BP thresholds for HT definition are maintained. However, as there are no proven beneficial effects of decreasing BP to levels lower than 140/90 mmHg, the 2014 Guidelines recommend, with grade A level, BP <150/90 mmHg for the general population aged more than 60 years.

ROLE OF SNS IN HYPERTENSIVE STATES

The sympathetic nervous system (SNS) is a hallmark of primary HT implicated not only in the development, perpetuation and severity of the disease but also in the pathophysiological consequences associated (heart and end-stage renal disease) (figure 2).[13,15] Nevertheless, only recently was its differential activation in the various organs established.[16]

This differential autonomic cardiovascular modulation can be quantified through microneurography or regional spillover method. The former measures postganglionic sympathetic nerve firing in the subcutaneous nerves (skin and skeletal muscle vasculature), giving immediate information on the electrical transmission. The regional noradrenaline (NA) spillover method is considered nowadays the gold standard.[13] This biochemical technique is a clinical index of organ-specific and overall SNS's activity since NA efflux into the venous system is proportional to SNS's firing rate. Consequently, during constant-rate infusion of radiolabeled NA (which takes into account NA uptake): regional NA spillover = $[(C_V - C_A) + C_AE] \times PF$, where C_V and C_A are the plasma concentrations of NA in regional venous and arterial plasma, respectively, E is the fractional extraction of radiolabeled NA in transit of blood through the organ, and PF is the organ plasma flow.[17]

The cardiac baroreflex sensitivity reduction in HT has been recognized in various studies, confirming the SNS effect on the heart.[18] There is also evidence of peripheral vasoconstriction related to SNS involvement. Additionally, measurement of kidney NA spillover revealed an increased activation of

sympathetic outflow with a mean elevation of 2 or 3 times the normal value.[13,16] Therefore, the hyperkinetic circulation profile is early established in HT development with raised resting heart rate (HR) and cardiac output, increased peripheral and renovascular resistance and elevated plasmatic levels of NA, independent of disease severity stage.[19]

The involvement of the renal SNS in the BP control is complex since it is simultaneously the receiver and originator of sympathetic signals by the efferent and afferent fibers, respectively, both located within the renal artery.[20]

The efferent renal sympathetic nerves are regulated by central sympathetic outflow, vagal tone and renorenal reflexes. These fibers affect renal function not only by inducing antinatriuresis through elevation of renin secretion via the juxtaglomerular apparatus (β1-adrenoceptors) but also by enhancing sodium and water reabsorption through activation of the Na^+/K^+ adenosine triphosphatase in the renal tubular cells (α1B-adrenoceptors). On the other hand, they also decrease GFR by inducing direct renal vasoconstriction (α1A-adrenoceptors) which decreases renal blood flow. However, there seems to be a graded response depending on the effect of the sympathetic signal on adrenoceptors' differential activation: low frequency stimulation only affects renin secretion whilst higher frequencies also influence sodium reabsorption and renal vascular tone.[23]

The afferent renal sympathetic nerves are stimulated by chemoreceptors in renal *interstitium* and mechanoreceptors in the renal wall. The former are sensitive to variations in electrolyte concentration and plasma osmolality and renal ischemia. The mechanoreceptors are stimulated by signaling changes in hydrostatic renal pelvic pressure.[20] The stimulation of these fibers modulates autonomic centers in the hypothalamus, the paraventricular nucleus, which increases (directly or through rostral ventrolateral medulla neurons' activation) the sympathetic outflow to the kidney and other organs involved in the cardiovascular control, contributing to the neurogenic elevation of BP.[13,15] Despite central sympathetic system's predominant role, raised BP is also influenced by peripheral adrenergic abnormalities as inappropriate neuronal reuptake of NA or peripheral α-

adrenoceptors' downregulation.[19] Consequently, through the influence on the regulation of overall sympathetic tone, afferent fibers have a predominant role in the genesis and maintenance of HT. Furthermore, these fibers are essential to preserve hydrolytic balance in case of unilateral excretion disorder since there is a direct communication with the contralateral kidney (renorenal reflex).[7]

Subsequently, neurogenic primary HT is considered to be responsible for more than 50% of all cases of high BP.[16] Although mechanisms of SNS overdrive are not completely understood, some hypotheses have been considered such as the impairment of volume-sensitive receptors or arterial chemoreceptors. Also, the contribution of humoral elements (insulin, angiotensin II) and the involvement of nutritional or behavioral features are suggested.[19]

RENAL SYMPATHETIC DENERVATION (RSD)

NEW TREATMENT FOR OLD DISEASE

HISTORICAL BASIS FOR RSD

SNS has been considered a possible therapeutic target in cases of RH since the early 20th century as its effect on vasoconstriction was already acknowledged. There were many surgical sympathectomy approaches with different removal extension.[24] According to Gulati and White[25], the radical lumbo-dorsal splanchnicectomy was firstly developed in 1938 by Smithwick. Despite being extremely effective in BP control with reported cardiac size reduction, renal function improvement, decreased incidence of precordial pain and cerebrovascular events and mortality rate[7], these procedures were associated with intolerable side effects like severe orthostatic hypotension, syncope, paradoxical excessive sweating, sphincter incontinence and erectile dysfunction. Moreover, the technique's significant invasiveness associated with the development of effective and better tolerable oral sympathetic-blocking drugs led to its abandonment.[26]

Nonetheless, it was an undisputable proof-of-concept of SNS overdrive in RH, confirming BP control's achievement through reduction in sympathetic tone. Besides, it revealed that adequate renal function is independent of intact renal SNS, confirmed by transplantation, since kidneys are still capable of maintaining electrolyte and volume homeostasis and adrenaline-mediated stress responses over time despite reduction in the sympathetic input.[27]

RENAL RADIOFREQUENCY ABLATION (RFA) PROCEDURE – PIONEERING WORK

Recently, RSD has been receiving additional interest as an HT therapeutic option not only because of sympathetic fibers' activation role (in particular renal network) in disease's progression and complications but also due to significant degree of SNS overdrive demonstrated in RH.[19,28] The development of a new endovascular approach was based on cardiac arrhythmias efficient treatment with percutaneous radiofrequency ablation (RFA)[24], aiming to avoid surgical denervation side effects and still achieve its success. Therefore, percutaneous renal RFA appears as a selective and minimally invasive procedure, with limited periprocedural risk and shorter recovery time.

The catheter-based RSD therapy using radiofrequency was firstly outlined by Krum et al in an international Proof-of-principle study[29] which included 50 patients with RH (table 3); 5 were excluded based on anatomical criteria. This group was followed-up during the trial and had comparable baseline patient characteristics (table 4). After renal artery angiography and heparin administration to achieve 250s activated clotting time, the "Symplicity" catheter was placed onto the distal renal artery wall via femoral artery. The catheter was connected to a radiofrequency generator which enabled energy delivery to endoluminal surface according to a predetermined algorithm and data on temperature, length of treatment and impedance, constantly monitored in order to prevent arterial injury. Radiofrequency energy, lower than that used for cardiac electrophysiological procedures, was delivered 4 to 6 times in each artery in a helical pattern lasting up to 2 minutes (figure 3).

The procedure was initially conducted in a 2-stage way (10 patients had contralateral artery ablation 1 month later). As safety was established, it became a simultaneous bilateral procedure. Both treatment compliance and maintenance were emphasized to patients and physicians, respectively.

In every visit after the procedure both office SBP and DBP revealed a significant decrease when compared to baseline ($p<0.05$). Although the extent of BP reduction is significantly different taking into account BP measurement method (table 4), office and ABPM decrease are strictly related. RFA efficiency was sustained even when medical treatment alterations were considered. Regardless the 12-month promising outcomes, 6 patients' BP decreased less than 10 mmHg (non-responders) which may point out to either ablation failure or SNS overdrive's secondary role in some cases of RH. However, the mean decrease in renal NA spillover rate of 47% in 10 patients 15-30 days after the procedure associated with the significant reduction of total body NA spillover in 1 patient[30] attested RSD effectiveness in kidney's both efferent and afferent sympathetic drive reduction.

No significant side effects were detected, both procedure-related renovascular damages (confirmed by 18 patients' 14-30 days angiogram and 14 patients' 6-month magnetic resonance angiogram) and renal function deterioration (GFR estimated in 25 patients). Only 2 surgical complications were identified which were immediately resolved: renal artery dissection through stenting and femoral artery aneurysm with antibiotics and analgesics. Also, the considerable amount of pain during the procedure (common pathway of sympathetic nerves and C pain fibers) led to a more aggressive control in the subsequent trials.[31]

RECENT CLINICAL EVIDENCE

- *Symplicity system and trials*

Despite being the first evidence of RSD's safety and efficiency, the small number of patients treated limited Proof-of-principle's relevance. Therefore, investigators decided to spread the therapeutic approach to 153 patients, including the patients already treated and increase the follow-up period to

36-month (Symplicity HTN-1 Trial).[32] After the first 12 months, patients were given the choice of a 24 or 36 months follow-up period, 111 of whom agreed on the second period. The respective baseline data, BP variations and complications are reported on table 4. BP control (<140 mmHg) was significantly augmented through the follow-up period, contrarily to the decrease of patients with SBP >180 mmHg (from 30% at baseline to 5% at 36-month). Although re-innervation was hypothesized, BP-lowering persisted and even augmented at 36-month when compared with 12-month decrease, without HR's significant alteration. One eventual explanation is the afferent renal fibers' probable role on central sympathetic overdrive, changing the baroreflex to lower homeostatic regulation point.[30,33] However, antihypertensive drug therapy's influence remains undetermined since it could be changed after the 12th month. No significant differences were detected in BP-lowering considering age, renal function or diabetes status. Despite being overall well preserved, the 10 patients' 24-month GFR revealed a decrease of 16 mL/min/1.73m^2.[34] Nevertheless, according to Sadowski et al (2011) quoting Bakris and Williams, RSD has a renoprotective effect since GFR decline is lower than it would be expected considering baseline SBP. The 3 deaths that occurred (1 myocardial infarction, 1 sudden death syndrome and 1 cardiac and respiratory arrest) were considered to be independent from the ablation procedure. No vascular alteration was detected at 6-month follow-up imaging (available in 81 patients)[34] and stenosis rate was really low. Consequently, the results of the expanded-cohort were the first to demonstrate not only a sustained BP reduction but also a preserved safety and maintained renal function 3 years after the procedure.

Nevertheless, Symplicity HTN-1 upholds Proof-of-study's weaknesses since they lack a control group (risk of placebo and Hawthorne effect) and both the RH definition (without screening of HT etiology and no BP measurement method established) and exclusion criteria are inadequate. Moreover, follow-up numbers remain reduced and the antihypertensive regime adjustments and adherence were not taken into account. The unblinded analysis might also lead to observer bias. Besides, selection bias cannot be excluded.[7,29,32,33,35]

Meanwhile, in order to validate the outcomes obtained, the Symplicity HTN-2[36], an international randomized clinical trial, recruited 190 patients according to inclusion criteria (table 3). After recording medication intake and BP values for 2 weeks, 106 of these were randomly distributed in 1:1 ratio to RSD or control groups, both continuing the previous antihypertensive treatment without adjustments except if medically required.

At baseline, patients' characteristics, mean BP and antihypertensive therapeutics between the two groups were identical. The primary endpoint was achieved in 49 of the treated patients (94.2%) and in 51 of the controls (94.4%), with a significantly different BP reduction between-group ($p<0.05$). However, once again these results differ from the 6-month 24h-ABPM (table 4). Six-month BP control (SBP <140 mmHg) was reached in 39% of RSD group compared to 6% of controls. Six-month SBP reduction ≥10 mmHg was also significantly different between-group. It is noteworthy to report the procedure's complete inefficiency (no BP reduction) in 5 of the treated patients (10%). The antihypertensive treatment's decrease was significantly different between groups: 20.4% in RSD and 5.9% in control group. Contrarily, pharmacological intensification was not. Besides, there was no significant alteration in renal function in both groups during the follow-up period.

Through 6-month imaging tests undertaken in 43 of the 49 patients no difference was detected in renal vascular anatomy. Although progression of a pre-existent atherosclerotic lesion was observed, it was placed away from the RSD ablation site. Bradycardia cases were successfully managed as well as the 5 minor periprocedure complications reported. Major complications during follow-up period were similar in both groups (table 4). Also, the occurrence of adverse effects was comparable between groups, without severe procedure or device-related complications in RSD group.

After the 6-month follow-up period, control patients were offered the RSD procedure as long as they maintained SBP ≥160 mmHg.[37] The crossover group (35 patients) had baseline demographic features and antihypertensive treatments comparable to the initial RSD group. This 12-month follow-up data exhibited not only persistence of significant BP reduction in the initial RSD group compared to

baseline (28/10 mmHg) but also an equivalent significant decrease in the crossover group: a variation of -24/-8 mmHg, comparable to the 6-month change in the initial interventional group (-32/-8 mmHg, p=0.15). Besides, therapy regimens' modifications were not significantly different between the initial RSD and the crossover groups. GFR remained stable in both groups. Also, safety was confirmed through only 1 case of artery dissection, 3 hypertensive and 1 hypotensive episodes and no deaths.

Symplicity HTN-2's results, notwithstanding being on behalf of previous findings, are still questionable due to similar previous limitations: non-double blinded analysis, incomplete exclusion criteria (no secondary HT screening) and small sample size and follow-up period, which may mask the development of complications. Despite being a randomized trial, group baseline characteristics like sex, diabetes and coronary artery disease rates are different leading to a severity discrepancy into RSD group. Besides, since baseline 24h-ABPM was not measured, white-coat HT was not excluded. Although the included patients had to carry out a 2-week antihypertensive therapy, there was no systematic adherence assessment during follow-up.[38-40]

RSD future trials need to respond to some of the questions brought up by past trials' limitations. It is Symplicity HTN-3's purpose[41], a multicenter randomized single-blinded trial conducted in America, with wider inclusion and exclusion criteria in order to assess RSD's both effectiveness and safety in true RH patients (table 5). Six-month both office-BP and 24h-ABPM are, respectively, primary and secondary efficiency outcomes, in order to clarify the differences observed in the previous trials. The 6-month incidence of major adverse effects is the primary safety outcome.

Following recruitment phase, in which were enrolled patients with SBP ≥160 mmHg while on stable treatment with 3 or more different drugs (including one diuretic) for no less than 2 weeks, there was the screening period with ABPM and therapy adherence registries for at least 2 weeks. Patients with sustained high SBP and mean 24h-ABPM ≥135 mmHg undertook selective renal angiography to verify

the accomplishment of anatomic criteria. 530 patients were posteriorly randomized in a 2:1 ratio to RSD or sham procedure, both continuing the previous medical treatment.

As a blinded study, patients were unaware of randomization attribution with similar follow-up in both groups. Moreover, staff measuring BP was also blinded throughout all trial. Before 6-month evaluation, which includes renal artery duplex imaging, patients recorded ABPM and therapy intake for 2 weeks. Follow-up period is 3 years for both groups.

The announcement made by Medtronic (symplicity system's producer) on January the 9th 2014 about Symplicity HTN-3's results tempered RSD enthusiasm on RH treatment. Despite guaranteeing primary safety endpoint, the primary efficacy endpoint (a sustained SBP reduction at 6-month) was not accomplished. (http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&id=1889335) According to Bakris, co-principal investigator, even though BP reduction was not statistically significant, the methodology used is far more rigorous than in previous trials. Therefore, despite believing European guidelines will be reformulated, he considers procedure's dismissal ethically unacceptable. (http://www.medscape.com/viewarticle/819018) Besides, Dr. Marco Valgimigli, on behalf of the ESC, argues the importance of having the complete data since treatment's efficacy is not determined by studies' primary endpoint success. These concepts are also supported by Dr. Sanjay Kaul. Other investigators consider Symplicity HTN-3's results as a possible failure's consequence of either procedure or Medtronic's device. (http://www.medpagetoday.com/Cardiology/Hypertension/43726) However, only through the final data will definite conclusions be defined.

- *Others Renal Sympathetic Denervation trials*

24h-BP profile has been recognized as organ damage independent prognostic factor. Despite not established, autonomic dysfunction seems to be the probable underlying mechanism. Taking into

account RSD's effect both on renal and total body sympathetic activity[30], Zuern et al hypothesized a similar outcome regarding 24h-BP variability.[42] Inclusion and exclusion criteria and methodology were comparable to Symplicity's. Six months after the procedure, the selected patients (n=11) revealed both an office-SBP decrease equivalent to previous trials (-30.4 mmHg, p=0.007) and a significant 24h-BP variability reduction (systolic coefficient of variation: from 0.11 to 0.09, p=0.041; diastolic coefficient of variation: from 0.14 to 0.11, p=0.024), more pronounced than 24h-ABPM decline (SBP from 149 to 142 mmHg, p=0.086; DBP from 82 to 79 mmHg, p=0.167).

SNS dysfunction is also a predictor of Chronic Kidney Disease's (CKD) development and progression as afferent and efferent renal fibers contribute to the sympathetic overactivity vicious cycle. Hence, 15 patients with concomitant RH and moderate to severe CKD underwent renal ablation.[43] 12-month results suggest not only RSD's efficacy and safety since BP was significantly reduced (Δ office-BP=-33/-19 mmHg) without procedure-related complications, but also maintenance of renal function (electrolyte and water homeostasis preserved; ΔGFR with $p>0.05$). Moreover, as all patients had baseline and follow-up 24h-ABPM, a significant effect on nocturnal BP was detected after only 3 months (ΔABPM night-time=-14/-8 mmHg, p=0.03/0.02), through physiologic dipping pattern reestablishment (p=0.01).

As BP reduction has enormous cardiovascular benefits (stroke, myocardial infarction, heart failure and death) RSD was recently performed in 20 cases of long-standing mild RH (even with 3 or more antihypertensive drugs, SBP=[140-160] mmHg) in order to determine procedure's efficacy and safety.[44] Six-month outcomes demonstrated office-SBP as well as mean systolic-ABPM significant decrease despite more modest than in Symplicity's patients, respectively, -13.1 mmHg ($p<0.01$) and -11.3 mmHg ($p<0.01$), associated with the absence of renal stenosis and preserved renal function (p=0.5). Therefore, further evidence is required to establish RSD as second-line therapy in mild RH.

In a multicenter national Portuguese registry, 78 patients were submitted to RSD, between July-2011 and November-2012, using both Symplicity (n=75) and EnligHTN (n=3) catheters. Among the included patients mean office-BP was 176.5/94.7 mmHg, most having HT for more than 10 years. Despite the fact that 2 cases of significant stenosis at the final angiogram and 2 pseudoaneurysms were detected, RSD's efficacy was proven by the 74% response rate in 23 patients with more than 6-month follow-up.[45] Already in September 2011 the procedure's feasibility was confirmed by a Portuguese two-case report.[46]

ABLATION CRITERIA

Nowadays, based on clinical trial's evidence, RSD via Symplicity catheter has been already approved in Australia[47], Europe[48] and Canada[49] exclusively for RH treatment in patients with preserved renal function (GFR ≥45 mL/min/1.73m^2). Therefore, only patients with raised office-SBP (≥160 mmHg or ≥150 mmHg in type 2 diabetes patients) despite the combination of at least 3 antihypertensive drugs (including one diuretic) and without contributing factors, like increasing BP substances or inappropriate lifestyles, are recommended to this procedure. Secondary HT causes must be excluded as well as non-compliance to antihypertensive treatment. Moreover, confirmation of high BP through 24h-ABPM is required in order to exclude white-coat HT. Although medical therapy may be optimized with association of mineralocorticoid receptor antagonist, prolonged treatment with this drug is restricted due to its adverse effects. An imaging test of the renal system should be realized before the procedure since it is recommended in renal arteries ≥ 4mm in diameter and ≥ 20 mm in length before any major branch bifurcation (figure 4).

As there is unsatisfactory clinical evidence, RSD is not recommended in cases of significant renal artery abnormalities (hemodynamically or anatomically), past renal interventions (angioplasty or stents), unstable clinical conditions (e.g. acute coronary event), pulmonary arterial HT, chronic

oxygen need, pregnancy, preeclampsia or children. Besides, this therapeutic approach should only be conducted in specialized centers fully equipped not only for diagnosis and procedure execution but also for complications management. It also requires infrastructure for a complete vigilance with constant follow-up assessments.[50]

PROSPECTIVE DEVELOPMENTS

Notwithstanding all the current questions, RSD through endovascular catheter has proved its influence in BP-lowering. Therefore, this therapeutic potential has led to an exponential development of new technological concepts (table 6) in order to exploit not only safety and efficiency with reduction of procedural time but also patient's comfort through pain reduction.[24,51]

Regarding RFA techniques, the most widely used is the Symplicity system. However, there are others systems using different catheters like EnligHTN multielectrode, Vessix Vascular V2 or OneShot already on trials that aim at reducing both BP and procedural time.[21,52] RSD has been proved effective through ThermoCool, an off-the-shelf saline-irrigated RFA catheter, which is able to significantly decrease 24h-ABPM (-21/-11 mmHg, p=0.003/0.005) and SNS metabolites' levels. As proved on cardiac electrophysiology ablation, this catheter is capable of minimizing the surface damage and increasing lesions' depth since it actively cools the electrode.[53]

Furthermore, this procedural improvement includes ultrasound as a more precise, quicker and less damaging ablative technique through both invasive and noninvasive procedures, also under development. Ultrasound energy consists in high-frequency sound waves being able to increase temperature at depth. The PARADISE catheter emits uniform circumferential ultrasound energy through the cylindrical transducer positioned inside the water balloon. This ultrasound ablation presented similar results to RFA's, decreasing not only non-target tissue's damage but also procedure's time.[54]

Another strategy is tissue-directed microinfusion of neurotoxins, such as guanethidine or vincristine, into the vessel wall and perivascular area, leading to a chemical sympathectomy without the adverse side effects of systemic delivery.[21,52]

However, all these approaches require long-term clinical data in order to correctly establish the most beneficial.[24]

ADDITIONAL EFFECTS

As SNS disorder is a systemic condition implicated in chronic diseases' development, RSD is expected to have further physiologic benefits. Beyond HT, SNS dysfunction has been established in heart failure's progression with β-blockers therapy as a survival prolonger.[55] In a recent hypertensive heart disease trial[56] 46 patients underwent RSD while 18 attended as control group. The RSD group exhibited not only marked reduction of left ventricular (LV) mass (from 112.4 g/m^2 at baseline to 94.9 g/m^2 at 6 months, $p<0.001$) but also significant improvement of both systolic and diastolic function at 6-month echocardiography evaluation, compared with baseline and controls' values (table 7). These results were associated with significant BP decrease. However, non-responders patients (BP reduction <10 mmHg) showed equally a significant decrease in LV mass and diastolic dysfunction which may emphasize RSD's influence on LV hypertrophy despite the lack of BP response.

An extension of Symplicity HTN-2[57], aiming at establishing RSD's effect on physical activity with a 3:1 randomization pattern, revealed BP reduction during exercise (from 226/104 mmHg at baseline to 205/99 mmHg at 3 months; $p<0.0001$ for SBP, $p=0.033$ for DBP) without chronotropic function compromise (HR at peak exercise decreased 3 bpm, $p=0.141$). Also, BP after exercise (limited by symptoms' development) and HR recovery improved in the 37 treated patients, -29/-8 mmHg ($p<0.002$) and +4 bpm ($p=0.009$), respectively.

Furthermore, RSD has been proved effective in HR reduction[58] directly related to baseline HR values ($p<0.05$ when baseline HR >60 bpm). Six months after RSD, no correlation was established between its effect on HR or other electrocardiographic parameters and on BP ($r=-0.102$, $p=0.369$). On the contrary, PR prolongation, which confirms systemic sympathetic activity's inhibition, is correlated with a more pronounced HR decrease. These breakthroughs are noteworthy since raised HR plays a major role in the pathogenesis of coronary disease, myocardial infarction, chronic heart failure and HT.

Insulin's role on SNS's activation through direct central stimulation is already acknowledged. However, it has also been proved that SNS influences metabolic disarray.[19] This potential effect on metabolic disorders was not only proved by fasting glucose, insulin and C-peptide levels' significant reduction, -9.4 mg/dL ($p=0.039$), -11.6 µIU/mL ($p=0.006$) and -2.3 ng/mL ($p=0.002$) respectively, but also by the significant increase in insulin sensitivity ($IS_{QUICKI}=+0.04$, $p=0.001$) in 37 patients 3 months after RSD, compared to unchangeable levels in control group.[59] This data confirms the bidirectional relationship between SNS overactivity and insulin resistance. Nevertheless, RSD's metabolic effects were not correlated with BP variation. Patients with obstructive sleep apnea and RH (n=10) revealed a metabolic control with improvement of hemoglobin A1C levels (from 6.1% to 5.6%, $p<0.05$) associated with BP (-34/-13 mmHg, $p<0.01$) and apnea-hypoapnea index reduction (from 16.3 to 4.5 events per hour, $p=0.059$) 6 months after RSD.[60]

Despite not being assertive, these indications are sufficient to promote future investigation of RSD's additional effects.

CONCLUSION

Gathering all the current evidence, RSD presents itself as a feasible, safe and clinically relevant procedure, able to significantly decrease BP levels in RH patients without important complications associated. Moreover, this technique has been proved effective in HT's associated complications with potential cardiac function improvement, HR decrease and metabolic control enhancement.

Since it is a recent interventional approach, most evidence assessing this procedure in humans comes from trials examining the efficacy and safety of the Symplicity Catheter System. Nevertheless, it has been submitted to great development with several endovascular catheters presenting different energy sources.

However, enthusiasm for this possibly revolutionary procedure must be tempered since data is still restricted due to trial's limitations which cast doubts about long-term durability or unpredictable effects development. Also, the discrepancy between office-BP and ABPM measurements raises the possibility of BP reduction being attributed to nonprocedural-related effects.

Aside these apprehensions, RSD is already considered the last resort treatment in some countries exclusively for patients with RH who have exhausted all other available medical management options.

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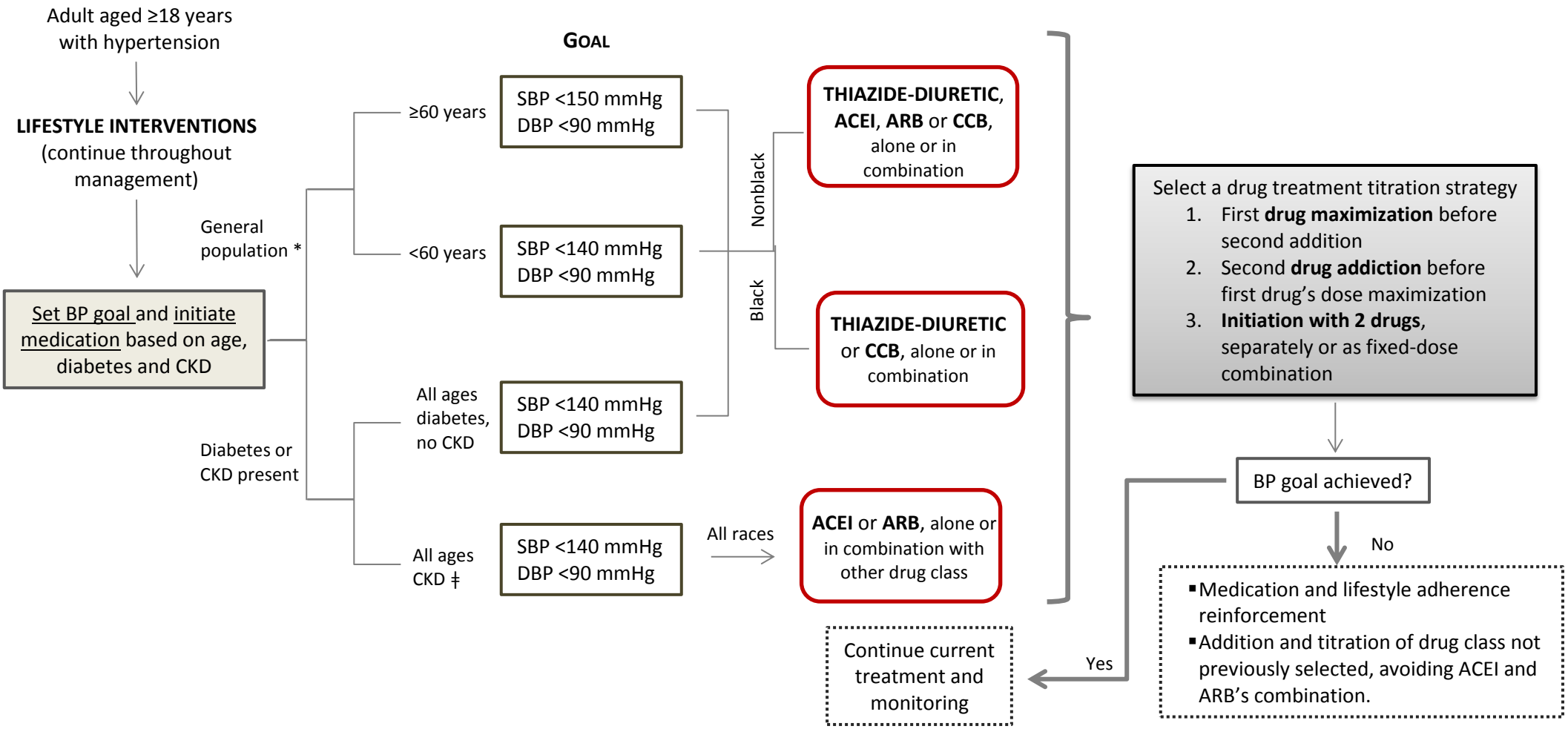

Fig. 1 - Algorithm for hypertension management. Adapted from James, Oparil and Carter (2013).[14] β-blockers are not recommended for HT's initial treatment since not only compared with the 4 recommended classes the results were similar in some studies but also stroke's incidence was higher compared with ARB. *No diabetes or CKD. ‡ with or without diabetes. ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; BP – blood pressure; CCB – calcium channel blockers; CKD – chronic kidney disease; DBP – diastolic blood pressure; SBP – systolic blood pressure.

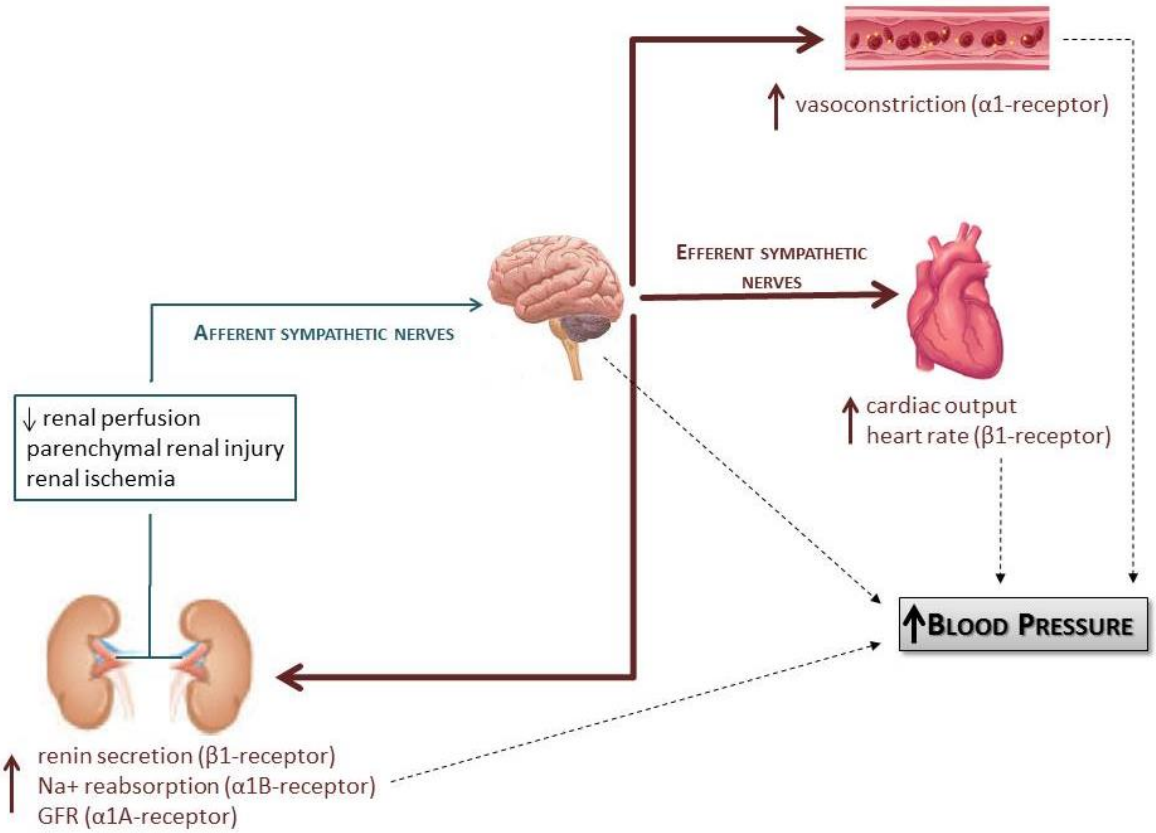

Fig.2 – Sympathetic nervous system role in Hypertension. Adapted from Bunte, Infante-Oliveira and Shishehbor (2013)[21]; Kanai and Krum (2013)[22]. GFR – glomerular filtration rate.

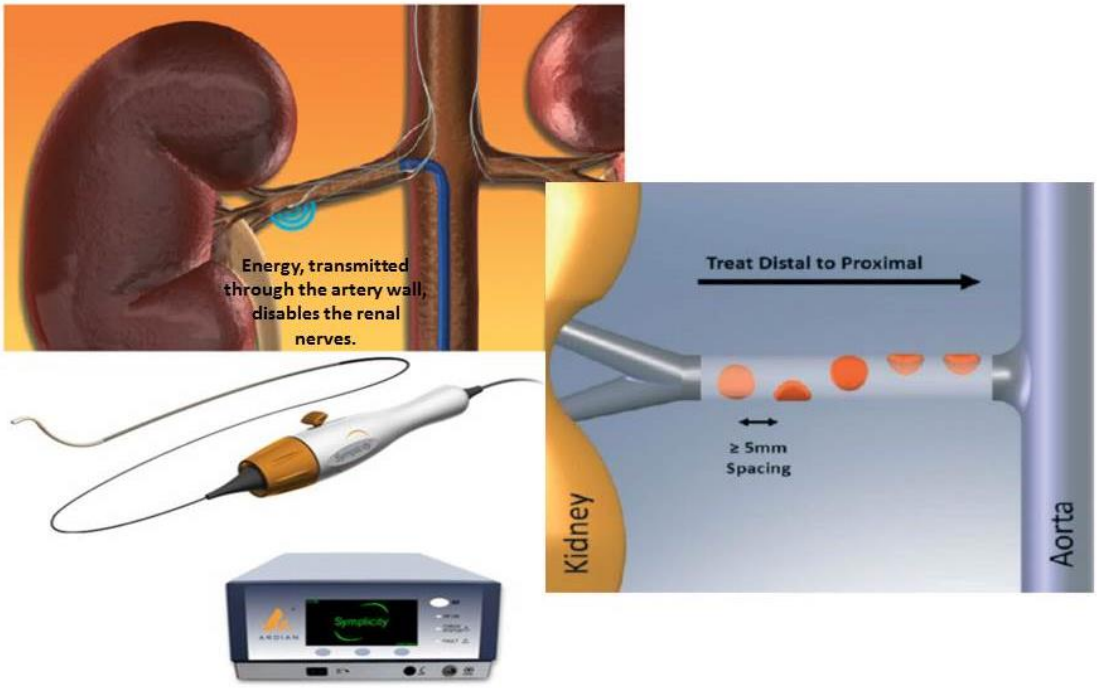

Fig.3 – The radiofrequency ablation procedure and simplicity cathether. Adapted from Kanai and Krum(2013)[22].

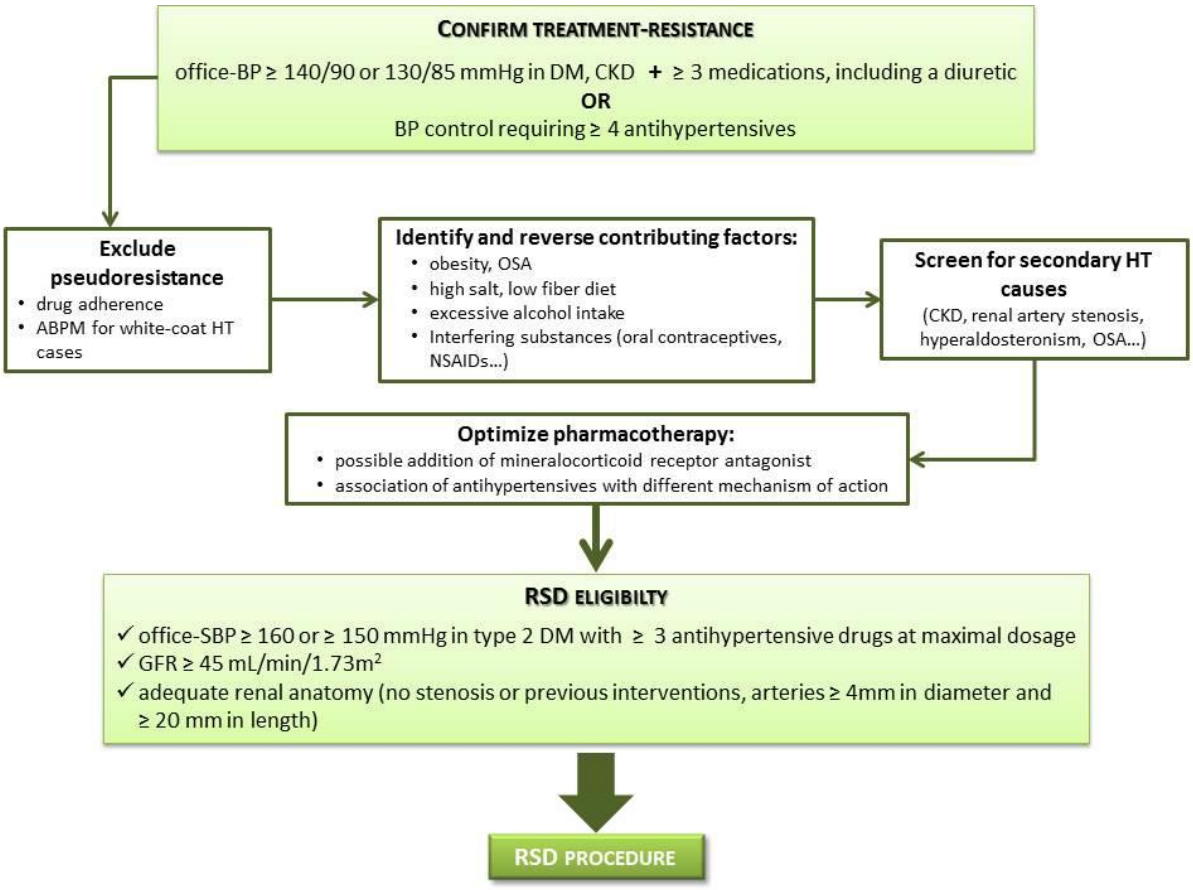

Fig.4 – Recommended pathway to determine patients' eligibility for Renal Sympathetic Denervation procedure. Adapted from Schlaich, Schmieder, Bakris et al(2013)[50]; Mahfoud, Luscher, Andersson et al(2013)[48]. ABPM – ambulatory blood pressure monitoring; BP – blood pressure; CKD – chronic kidney disease; DM – diabetes mellitus; GFR – glomerular filtration rate; HT- hypertension; NSAID's – non-steroidal anti-inflammatory drugs; OSA – obstructive sleep apnea; RSD – renal sympathetic denervation; SBP – systolic blood pressure.

FIGURE LEGENDS

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Table 1 – Patients characteristics associated with hypertension treatment-resistance

RISK FACTORS
▪ excessive sodium intake
▪ excessive alcohol consumption
▪ physical inactivity
▪ female sex
▪ African race
▪ advanced age
▪ higher baseline BP (specially systolic)
▪ chronic renal disease
▪ obesity
▪ diabetes
▪ presence of left ventricular hypertrophy
▪ medications that increase BP or decrease antihypertensive agents effect
▪ inadequate therapy
▪ HT secondary causes

Adapted from Calhoun et al (2008)[3] and UpToDate (2013). BP – blood pressure; HT – hypertension.

Table 2 – Pharmacological treatment of Hypertension

	ANTIHYPERTENSIVES †	COMPELLING CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS	CONDITIONS IN WHICH ARE PREFERRED	
ACE INHIBITORS	Captopril, Enalapril, Fosinopril, Imidapril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril, Zofenopril	Pregnancy, bilateral renal artery stenosis angioneurotic oedema, hyperkalaemia,	Women with child bearing potential	LVH Microalbuminuria Renal dysfunction Previous MI	Metabolic syndrome Diabetes mellitus Asymptomatic atherosclerosis ‡ Peripheral artery disease ‡
ARB	Telmisartan, Irbesartan, Candersartan, Losartan, Valsartan, Eprosartan	Pregnancy, hyperkalaemia, bilateral renal artery stenosis	Women with child bearing potential	HF	
B-BLOCKERS	Bisoprolol, Nebivolol, Carvedilol, Celiprolol, Atenolol, Metoprolol	Asthma, A–V block (grade 2 or 3)	Metabolic syndrome, glucose intolerance, athletes and physically active patients, COPD	Previous MI Angina pectoris HF	AF (ventricular rate control) Pregnancy
CALCIUM CHANNEL	<u>NONDIHYDROPYRIDINES</u> Verapamil, Diltiazem	A–V block (grade 2 or 3, trifascicular block), severe LV dysfunction, HF		LVH ISH (elderly) Angina pectoris Black population Pregnancy	Peripheral artery disease Metabolic syndrome Asymptomatic atherosclerosis AF (ventricular rate control) *
	<u>DIHYDROPYRIDINES</u> Amlodipine,		Tachyarrhythmia HF		

Table 2 – Pharmacological treatment of Hypertension (continuation)

	ANTIHYPERTENSIVES †	COMPELLING CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS	CONDITIONS IN WHICH ARE PREFERRED	
DIURETICS	THIAZIDE-TYPE Chlorthalidone, Indapamide, Hydrochlorothiazide	Gout		HF ISH (elderly)	Black population
	MINERALOCORTICOID RECEPTOR ANTAGONISTS Spironolactone, Eplenerone	Acute or severe renal failure (eGFR <30 mL/min), hyperkalaemia	Metabolic syndrome, glucose intolerance, pregnancy, hypercalcemia, hypokalaemia	HF	

Adapted from ESC/ESH Guidelines (2013)[1] and JNC8 Guidelines (2014)[14]. ACE – angiotensin-converting enzyme; AF – atrial fibrillation; ARB – angiotensin receptor blockers; A-V – atrio-ventricular; COPD – chronic obstructive pulmonary disease; eGFR – estimated glomerular filtration rate; HF – heart failure; ISH – Isolated systolic hypertension; LV – left ventricular; LVH – left ventricular hypertrophy; MI – myocardial infarction. † - Only some examples of several classes; ǂ - not angiotensin receptor blockers; * - not dihydropyridines.

Table 3 – Proof-of-Principle, Symplicity HTN-1 and Symplicity HTN-2's study characteristics

	Type of study	Inclusion Criteria	Exclusion criteria	Outcomes	Follow-up
PROOF – OF –PRINCIPLE	Observational study **50 patients**	▪SBP ≥ 160 mmHg with ≥ 3 antihypertensive drugs (1 diuretic) ▪confirmed intolerance to medications ▪GFR ≥ 45 mL/min/1.73m^2 ▪≥ 18 years ▪not pregnant ▪secondary HT cause excluded	▪type 1 diabetes ▪hemodynamically significant valvular disease ▪implanted pacemakers ▪renovascular abnormalities (renal artery stenosis, previous renal stent or angioplasty, dual renal or polar arteries) ▪on treatment with: clonidine, monoxidine, rilmenidine, warfarin	**Primary:** ▪BP reduction and procedural safety **Secondary:** ▪NA release and renal function	12 months
SYMPLICITY HTN-1	Observational study **153 patients**			**Primary** ▪durability of BP-lowering effects ▪ late adverse vascular or renal effects	36 months
SYMPLICITY HTN-2	Randomized control trial (1:1 ratio) **106 patients**	▪SBP ≥ 160 or ≥ 150 mmHg in type 2 diabetics with ≥ 3 antihypertensive drugs ▪2-week twice daily BP measurement and medication recording ▪GFR ≥ 45 mL/min/1.73m^2 ▪18-85 years	▪type 1 diabetes ▪substantial stenotic valvular heart disease ▪renovascular abnormalities (major stenosis, previous intervention, precluding anatomy) ▪contraindications to MRI ▪history of MI, unstable angina or cerebrovascular accident in the last 6 months ▪pregnancy	**Primary:** ▪ office-SBP difference between-group **Secondary:** ▪procedural safety (acute and chronic) ▪composite CV endpoint ▪SBP reduction ≥ 10mmHg ▪24h-ABPM and home-based BP change	6 months

ABPM – ambulatory blood pressure monitoring; BP – blood pressure; CV – cardiovascular; GFR – glomerular filtration rate; HT – Hypertension; MI – myocardial infarction; MRI – magnetic resonance imaging; NA – noradrenaline; SBP – systolic blood pressure.

Table 4 – Proof-of-study, Symplicity HTN-1 and Symplicity HTN-2's results

	Mean baseline values	Mean office-BP change		Non-responders*	ABPM change	Complications
PROOF -OF-PRINCIPLE	**RSD group (n=45)** ▪BP=177/101 mmHg ▪GFR=81 mL/min/1.73m^2 ▪4.7 antihypertensive drugs	▪1st ▪3rd ▪6th ▪9th ▪12th	-14/-10 (n=41) -21/-10 (n=39) -22/-11 (n=26) -24/-11 (n=20) -27/-17 (n=9)	13% (6 patients)	▪ -11 mmHg (9 responders) ▪ 10 mmHg (3 non-responders) ‡	▪1 renal artery dissection (not procedure related) ▪1 femoral pseudoaneurysm
	Control group (n=5) ▪BP=173/98 mmHg ▪GFR=95 mL/min/1.73m^2 ▪4.6 antihypertensive drugs	▪1st ▪3rd ▪6th ▪9th	+3/-2 (n=5) +2/+3 (n=5) +14/+9 (n=5) +26/+17 (n=2)			
SYMPLICITY HTN-1	▪BP=175/98 mmHg ▪GFR=85 mL/min/1.73m^2 ▪5.1 antihypertensive drugs	▪1st ▪6th ▪12th ▪24th ▪36th	-19/-9 (n=141) -22/-10 (n=144) -27/-14 (n=132) -29/-14 (n=105) -32/-14 (n=88)	7% (6 patients)		▪8 operative bradycardia ▪1 renal artery dissection (not procedure related) ▪3 femoral pseudoaneurysms ▪renal stenosis: 2 progressions of pre-existing stenosis; 2 new cases (1 of 80% → needed stent) ▪2 hypotensive events (unrelated to RSD); 2 orthostatic hypotension episodes (same patient); 13 hypertensive episodes; 1 acute tubular necrosis

Table 4 – Proof-of-study, Symplicity HTN-1 and Symplicity HTN-2's results (continuation)

	Mean baseline values	Mean office-BP change		Non-responders*	ABPM change	Complications
SYMPLICITY HTN-2	**RSD group (n=52)** ▪BP=178/96 mmHg ▪GFR=77 mL/min/1.73m^2 ▪5.2 antihypertensive drugs	▪1st ▪3rd ▪6th	-20/-7 (n=52) -24/.8 -32/-12 (n=49)	16.3% (8 patients)	▪ -11/-7 mmHg (20 patients)	▪7 operative bradycardia; ▪periprocedural (1 of each): hypotension, back pain, idiopathic paresthesia, urinary infection, femoral pseudoaneurysm ▪progression of pre-existing stenosis ▪5 HE (3 RSD + 2 control); 3 TIA (1 RSD + 2 control); 2 anginas (1 in each group)
	Control group (n=54) ▪BP=178/97 mmHg ▪GFR=86 mL/min/1.73m^2 ▪5.3 antihypertensive drugs	▪1st ▪3rd ▪6th	0/0 (n=54) -4/-2 +1/0 (n=51)	64.7% (33 patients)	▪ -3/-1 mmHg (25 patients)	

ABPM – ambulatory blood pressure monitoring; BP – blood pressure; GFR – glomerular filtration rate; HE – hypertensive emergencies; RSD – renal sympathetic denervation; TIA – transient ischemic attack. * Non-responders: minimal systolic blood pressure reduction (< 10 mmHg); ǂ: patients with ABPM at baseline and at follow-up longer than 30 days after procedure.

Table 5 – Symplicity HTN-3

INCLUSION CRITERIA	EXCLUSION CRITERIA	EFFECTIVENESS ENDPOINTS	SAFETY ENDPOINTS
▪18-80 years ▪office-SBP ≥160 mmHg (initial and confirmatory screening) ▪stable medication regimen for at least 2 weeks before initial screening and no changes planned for 6 months ▪written informed consent	▪renovascular ineligibilities (diameter <4mm or length <20mm; multiple renal arteries; stenosis>50% or aneurysm; previous interventions) ▪GFR <45 mL/min/1.73m^2 ▪average ABPM <135 mmHg ▪pregnancy, nursing ▪chronic oxygen support or mechanical ventilation beyond night ▪primary pulmonary HT, type 1 DM, pheochromocytoma, cushing's disease, hyperthyroidism, hyperparathyroidism, coarctation of aorta, severe cardiac valve stenosis ▪MI, unstable angina, syncope or cerebrovascular accident (prior 6 months) ▪planned surgery or CV intervention in the next 6 months ▪history of dependency, inability to comprehend instructions, unable to comply with trial's requirements	**Primary** ▪office-SBP change **Secondary** ▪average 24h-ABPM change ▪incidence of: SBP reduction ≥10, 15, 20 mmHg; SBP control (<140 or 130 mmHg in DM and RD); medication changes; home-BP change ▪12, 18, 24 and 36-month BP change	**Primary** ▪major adverse events (MAE) incidence (composite of many events) ▪new renal artery stenosis >70% (6-month angiography) Secondary: ▪each component of MAE ▪chronic safety ▪change in renal function

ABPM – ambulatory blood pressure monitoring; CV – cardiovascular; DM – Diabetes Mellitus; GFR – glomerular filtration rate; HT – Hypertension; MI – myocardial infarction; RD – renal disease; SBP – systolic blood pressure.

Table 6 – Overview of Renal Denervation systems

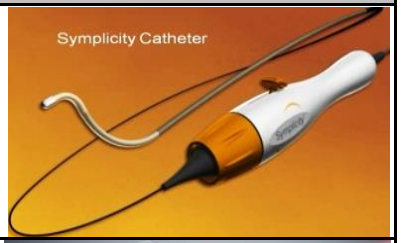
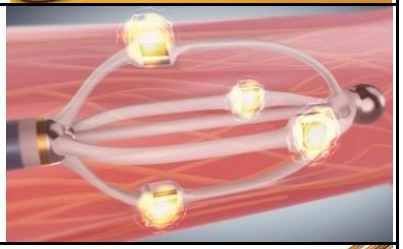
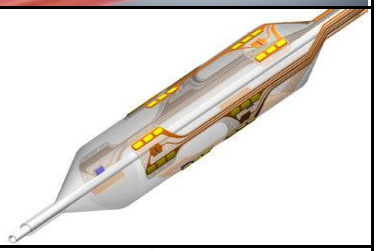
PRODUCT NAME AND SPONSOR	DESIGN	OPERATING MODE ?	CLINICAL TRIAL	
RADIOFREQUENCY ABLATION				
Symplicity catheter Medtronic Inc.	Single-electrode catheter	Multiple rotations through spiral pattern	Symplicity HTN 1-3; Renal Nerve Ablation in CKD patients; RDN in patients with RH and OSA	
EnligHTN catheter St. Jude Inc.	Multi-electrode catheter	Simultaneous energy delivery to 4 sites along arterial surface	ARSENAL	
Vessix V2 catheter Vessix Vascular Inc.	Balloon-mounted catheter	Low-pressure balloon with superficial bipolar electrodes	REDUCE-HTN	
OneShot catheter Maya Medical Inc.	Irrigated balloon-mounted catheter	Energy delivery by spiral electrode with cooling irrigation holes	RAPID	

Table 6 – Overview of Renal Denervation systems (continuation)

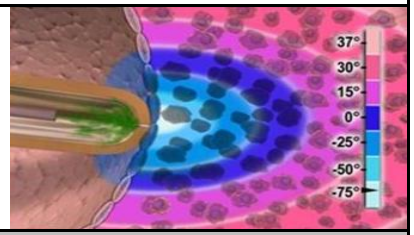
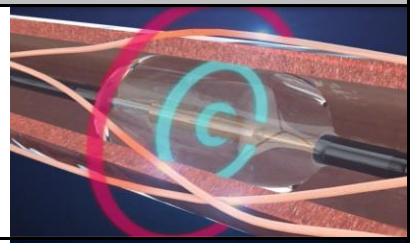
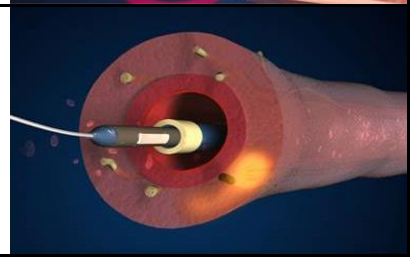
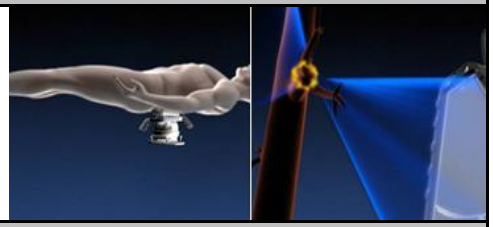
PRODUCT NAME AND SPONSOR	DESIGN	OPERATING MODE ?	CLINICAL TRIAL	
RADIOFREQUENCY ABLATION				
ThermoCool cryoablative catheter † Biosense Webster Inc.	Irrigated catheter	Constant preset energy delivery with maintenance of lower temperatures	SWAN HT; SAVE; RELIEF	
Chilli II cryoablative catheter † Boston Scientific Inc.	Irrigated catheter		SAVE	
ULTRASONIC ABLATION				
PARADISE catheter ReCor Medical Inc.	US balloon catheter	Circumferential energy by inflatable balloon with cooled fluid flow	REALISE	
TIVUS catheter Cardiosonic Ltd.	US autoregulating balloon catheter	High-intensity, non-focused, self-regulating ablation	ǂ	

Table 6 – Overview of Renal Denervation systems (continuation)

PRODUCT NAME AND SPONSOR	DESIGN	OPERATING MODE ?	CLINICAL TRIAL	
ULTRASONIC ABLATION				
Kona medical US system Kona Medical Inc.	Low intensity external US ablation catheter	Non-invasive low-intensity focused energy with imaging modality	ǂ	
TISSUE-DIRECTED PHARMACOLOGICAL ABLATION				
Bullfrog micro-infusion catheter Mercator MedSystems Inc.	Microneedle-equipped balloon catheter	Perivascular direct delivery of neurotoxins	ǂ	

Adapted from Bunte, Oliveira-Infante and Shishehbor (2013).[21] ARSENAL – Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patient trial; CKD – chronic kidney disease; HTN – Hypertension; OSA – obstructive sleep apnea; PARADISE – ReCor Percutaneous Renal Denervation System catheter; RAPID – Rapid Renal Sympathetic Denervation for Resistant Hypertension trial; RDN – Renal Denervation; REALISE – Renal Denervation by Ultrasound Transcatheter Emission trial; REDUCE-HTN – Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter; RELIEF – Renal Sympathetic Denervation for the Management of Chronic Hypertension trial; RH – resistant hypertension; SAVE – Impact of Renal Sympathetic Denervation on Chronic Hypertension study; SWAN HT – Renal Sympathetic Modification in Patients With Essential Hypertension study; SYMPLICITY HTN-1 – SYMPLICITY I: One-Year Results Following Sympathetic Renal Denervation in Refractory Hypertension trial; SYMPLICITY HTN-2 – Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension trial; SYMPLICITY HTN-3 – Renal Denervation in Patients With Uncontrolled Hypertension trial; TIVUS – therapeutic intravascular ultrasound; † - unknown mechanism; ǂ - under development

Table 7 – RSD's effect on left ventricular hypertrophy and cardiac function

		HEMODYNAMIC		LV HYPERTROPHY		SYSTOLIC FUNCTION		DIASTOLIC FUNCTION				
		SBP/DBP (mmHg)	HRR (bpm)	LV mass/BSA (g/m^2)	IV septum thickness (mm)	LV end-systolic volume (mL)	LV ejection fraction (%)	Mitral E-wave deceleration (ms)	Isovolumic relaxation time (ms)	Diastolic relaxation velocity * (cm/s)	LV filling pressure ǂ	LA size (mm)
RSD group (n=48)	Baseline	180.7/95.8	66.5	112.4	14.1	32.8	63.1	227.2	109.1	8.1	9.9	45.2
	6 month	152.9/87.0 (p<0.001)	60.9	94.9 (p<0.001)	12.5 (p=0.009)	25.6 (p=0.001)	70.1 (p=0.001)	185.2 (p=0.013)	85.6 (p=0.006)	9.9 (p=0.001)	7.4 (p=0.001)	42.5 (p<0.001)
Controls (n=18)	Baseline	184.5/98.2	66.3	114.8	14.2	31.1	64.3	236.0	119.4	6.6	10.9	43.7
	6 month	182.8/99.8	64.3	118.7	14.2	31.8	62.9	233.4	11.6	6.3	12.1	46.0
p for trend †		0.0396/0.041	0.047	0.004	0.032	0.015	0.048	0.008	<0.001	0.023	0.001	0.021

Adapted from Brandt et al(2012)[56]. BSA – body surface area; DBP – diastolic blood pressure; HRR – heart rate at rest; IV – interventricular; LA – left atrium; LV – left ventricular; RSD – renal sympathetic denervation; SBP – systolic blood pressure.* of the lateral mitral annulus; ǂ ratio of mitral inflow velocity to annular relaxation velocity); † differential efficacy between RSD and control group.

ANEXOS

Normas de publicação da Revista Portuguesa de Cardiologia

A Revista Portuguesa de Cardiologia, órgão oficial da Sociedade Portuguesa de Cardiologia, é uma publicação científica internacional destinada ao estudo das doenças cardiovasculares. Publica artigos em português na sua edição em papel e em português e inglês na sua edição online, sobre todas as áreas da Medicina Cardiovascular. Se os artigos são publicados apenas em inglês, esta versão surgirá simultaneamente em papel e online. Inclui regularmente artigos originais sobre investigação clínica ou básica, revisões temáticas, casos clínicos, imagens em cardiologia, comentários editoriais e cartas ao editor. Para consultar as edições online deverá aceder através do link www.revportcardiol.org.

Todos os artigos são avaliados antes de serem aceites para publicação por peritos designados pelos Editores (peer review). A submissão de um artigo à Revista Portuguesa de Cardiologia implica que este nunca tenha sido publicado e que não esteja a ser avaliado para publicação noutra revista.

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Os autores dos artigos aceitam a responsabilidade definida pelo Comité Internacional dos Editores das Revistas Médicas (consultar www.icmje.org).

Os trabalhos submetidos para publicação na Revista Portuguesa de Cardiologia devem respeitar as recomendações internacionais sobre investigação clínica (Declaração de Helsínquia da Associação Médica Mundial, revista recentemente) e com animais de laboratório (Sociedade Americana de Fisiologia). Os estudos aleatorizados deverão seguir as normas CONSORT.

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Declaração de originalidade

O autor deverá enviar uma declaração de originalidade. Ver anexo I

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Os dados de carácter pessoal que se solicitam vão ser tratados num ficheiro automatizado da Sociedade Portuguesa de Cardiologia (SPC) com a finalidade de gerir a publicação do seu artigo na Revista Portuguesa de Cardiologia (RPC). Salvo indique o contrário ao enviar o artigo, fica expressamente autorizado que os dados referentes ao seu nome, apelidos, local de trabalho e correio eletrónico sejam publicados na RPC, bem como no portal da SPC (www.spc.pt) e no portal online www.revportcardiol.org, com o intuito de dar a conhecer a autoria do artigo e de possibilitar que os leitores possam comunicar com os autores.

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NOTA IMPORTANTE! Para que se possa iniciar o processo de avaliação, o documento com o corpo do artigo deverá incluir todos os elementos que fazem parte do artigo: Títulos em português e em inglês; autores; proveniência; palavras-chave e keywords; Resumos em português e em inglês; Corpo do artigo, incluindo as tabelas; bibliografia; legendas das figuras e das tabelas.

1. Artigos Originais

Apresentação do documento:

- Com espaço duplo, margens de 2,5 cm e páginas numeradas.
- Não deverão exceder 5.000 palavras, contadas desde a primeira à última página, excluindo as tabelas.

• Consta de dois documentos: primeira página e manuscrito

• O manuscrito deve seguir sempre a mesma ordem: a) resumo estruturado em português e palavras-chave; b) resumo estruturado em inglês e palavras-chave; c) quadro de abreviaturas em português e em inglês; d) texto; e) bibliografia; f) legendas das figuras; g) tabelas (opcional) e h) figuras (opcional)-

Primeira página

Título completo (menos de 150 caracteres) em português e em inglês.

Nome e apelido dos autores pela ordem seguinte: nome próprio, seguido do apelido (pode conter dois nomes)

Proveniência (Serviço, Instituição, cidade, país) e financiamento caso haja.

Endereço completo do autor a quem deve ser dirigida a correspondência, fax e endereço eletrónico.

Faz-se referência ao número total de palavras do manuscrito (excluindo as tabelas).

Resumo estruturado

O resumo, com um máximo de 250 palavras, está dividido em quatro partes: *a)* Introdução e objetivos; *b)* Métodos; *c)* Resultados e *d)* Conclusões. Deverá ser elucidativo e não inclui referências bibliográficas nem abreviaturas (exceto as referentes a unidades de medida).

Inclui no final três a dez palavras-chave em português e em inglês. Deverão ser preferencialmente selecionadas a partir da lista publicada na Revista Portuguesa de Cardiologia, oriundas do Medical Subject Headings (MeSH) da National Libray of Medicine, disponível em: www.nlm.nihgov/mesh/meshhome.html.

O resumo e as palavras-chave em inglês devem ser apresentados da mesma forma.

Texto

Deverá conter as seguintes partes devidamente assinaladas: *a)* Introdução; *b)* Métodos; *c)* Resultados; *d)* Discussão e *e)* Conclusões. Poderá utilizar subdivisões adequadamente para organizar cada uma das secções.

As abreviaturas das unidades de medida são as recomendadas pela RPC (ver Anexo II).

Os agradecimentos situam-se no final do texto.

Bibliografia

As referências bibliográficas deverão ser citadas por ordem numérica no formato 'superscript', de acordo com a ordem de entrada no texto. As referências bibliográficas não incluem comunicações pessoais, manuscritos ou qualquer dado não publicado. Todavia podem estar incluídos, entre parêntesis, ao longo do texto. São citados abstracts com menos de dois anos de publicação, identificando-os com [abstract] colocado depois do título. As revistas médicas são referenciadas com as abreviaturas utilizadas pelo Index Medicus: List of Journals Indexed, tal como se publicam no número de Janeiro de cada ano. Disponível em: http://www.ncbi.nlm.nih.gov/entrez/citmatch_help.html#JournalLists. O estilo e a pontuação das referências deverão seguir o modelo Vancouver 3.

Revista médica: Lista de todos os autores. Se o número de autores for superior a três, incluem-se os três primeiros, seguidos da abreviatura latina et al. Exemplo:

17. Sousa PJ, Gonçalves PA, Marques H et al. Radiação na AngioTC cardíaca; preditores de maior dose utilizada e sua redução ao longo do tempo. Rev Port cardiol, 2010; 29:1655-65

Capítulo em livro: Autores, título do capítulo, editores, título do livro, cidade, editora e páginas. Exemplo:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. En: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American 1995. P79-96.

Livro: Cite as páginas específicas. Exemplo:

30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993. P. 33.

Material electrónico: Artigo de revista em formato eletrónico. *Exemplo:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts it an advisory role. Am J Nurs. [serie na internet.] 2002 Jun citado 12 Ago 2002:102(6): [aprox. 3] p. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

A Bibliografia será enviada como texto regular, nunca como nota de rodapé. Não se aceitam códigos específicos dos programas de gestão bibliográfica.

Figuras

As figuras correspondentes a gráficos e desenhos são enviadas no formato TIFF ou JPEG de preferência, com uma resolução nunca inferior a 300 dpi e utilizando o negro para linhas e texto. São alvo de numeração árabe de acordo com a ordem de entrada no texto.

- A grafia, símbolos, letras, etc, deverão ser enviados num tamanho que, ao ser reduzido, os mantenha claramente legíveis. Os detalhes especiais deverão ser assinalados com setas contrastantes com a figura.
- As legendas das figuras devem ser incluídas numa folha aparte. No final devem ser identificadas as abreviaturas empregues por ordem alfabética.
- As figuras não podem incluir dados que dêem a conhecer a proveniência do trabalho ou a identidade do paciente. As fotografias das pessoas devem ser feitas de maneira que estas não sejam identificadas ou incluir-se-á o consentimento por parte da pessoa fotografada.

Tabelas

São identificadas com numeração árabe de acordo com a ordem de entrada no texto. Cada tabela será escrita a espaço duplo numa folha aparte.

• Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.

• O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

2. Artigos de Revisão

Nº máximo de palavras do artigo sem contar com o resumo e quadros- 5.000

Nº máximo de palavras do Resumo - 250

Nº máximo de Figuras - 10

Nº máximo de quadros - 10

Nº máximo de ref. bibliográficas - 100

3. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

• Com espaço duplo, com margens de 2,5 cm.

• O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.

• Não podem exceder as 800 palavras.

• Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

4. Casos Clínicos

Devem ser enviados sob esta rubrica.

• A espaço duplo com margens de 2,5 cm.

• O título (em português e em inglês) não deve exceder 10 palavras

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5. Imagens em Cardiologia

• A espaço duplo com margens de 2,5 cm.

• O título (em português e em inglês) não deve exceder oito palavras

• Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

• O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

• Contêm um número máximo de quatro figuras.

Normas de publicação da revista portuguesa de cardiologia

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A Revista Portuguesa de Cardiologia aceita o envio de material eletrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material eletrónico adicional diretamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á eletronicamente no formato da sua receção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	FORMATO	EXTENSÃO	DETALHES
TEXTO	Word	.doc ou docx	Tamanho máximo 300 Kb
IMAGEM	TIFF	.tif	Tamanho máximo 10 Mb
AUDIO	MP3	.mp3	Tamanho máximo 10 Mb
VÍDEO	WMV	.wmv	Tamanho máximo 30 Mb